Site visit inspection report on compliance with HTA minimum standards

Southampton General Hospital

Proposed HTA licensing number 22674

Application to be licensed for the

- **procurement and testing of human tissues and cells for human application under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended)**

10 July 2019

Summary of inspection findings

The HTA found the proposed Designated Individual and the Licence Holder to be suitable in accordance with the requirements of the legislation.

Although the HTA found that Southampton General Hospital (the establishment) had met the majority of the HTA standards, six minor shortfalls relating to the governance and quality systems and premises, facilities and equipment standards were identified. These relate to the absence of a documented training programme, requirements for data retention times, the documented procedure for collecting blood for HTLV-I testing, the documented procedure for serious adverse events and reactions (SAEARs) reporting in accordance with the regulatory requirements and the scope of risk assessments.

The HTA's regulatory requirements

Prior to the grant of a licence, the HTA must assure itself that the Designated Individual, Licence Holder, premises and practices are suitable.

The statutory duties of the Designated Individual are set down in Section 18 of the Human Tissue Act 2004. They are to secure that:

- the other persons to whom the licence applies are suitable persons to participate in the carrying-on of the licensed activity;
- suitable practices are used in the course of carrying on that activity; and
- the conditions of the licence are complied with.

The HTA developed its licensing standards with input from its stakeholders. They are designed to ensure the safe and ethical use of human tissue and the dignified and respectful treatment of the deceased. The HTA inspects the establishments it licences against four groups of standards:

- consent
- governance and quality systems
- premises facilities and equipment
- disposal.

This is an exception-based report: only those standards that have been assessed as not met are included. Where the HTA determines that a standard is not met, the level of the shortfall is classified as 'Critical', 'Major' or 'Minor' (see Appendix 2: Classification of the level of shortfall). Where HTA standards are fully met, but the HTA has identified an area of practice that could be further improved, advice is given to the DI.

Reports of HTA inspections carried out from 1 November 2010 are published on the HTA's website.

Proposed licensable activities to be carried out by the establishment

'E' = Establishment has applied for a licence to carry out this activity.

Tissue Category; Tissue Type	Procurement	Processing	Testing	Storage	Distribution	Import	Export
Other; Cartilage (ATMP)	**E**		**E**				

Background to the establishment and description of inspection activities undertaken

Southampton General Hospital (the establishment) is one of several hospitals operated by University Hospital Southampton NHS Foundation Trust (UHS). The establishment has applied to be licensed for procurement and testing under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended). Specifically, the establishment proposes to procure cartilage as a starting material for an Advanced Therapy Medicinal Product (ATMP). The procedure known as autologous chondrocyte implantation (ACI) involves the expansion of chondrocytes by the ATMP manufacturer, followed by implantation of the expanded product into the donor to treat damaged knee cartilage. The establishment has an agreement with an ATMP manufacturer based in Germany.

Three Consultant Orthopaedic surgeons will undertake the ACI procedures. Potential patients will be identified by the Consultant Orthopaedic surgeons and reviewed using the online National audit tool which assesses patients against defined eligibility criteria. Donors will be provided with information to ensure they are fully informed regarding the procedure and the requirements for serology testing. Two consent forms will be used; one supplied by the Trust and the second by the ATMP manufacturer.

The establishment proposes to store three ACI kits, supplied by the ATMP manufacturer, within a temperature monitored theatre store room; the unique kit number, expiry date, date / time of receipt and the name of the theatre personnel receiving the kits will be recorded in a traceability register. Blood samples for the mandatory serology testing will be taken on the day of procurement of the cartilage biopsy. All tests for the mandatory serology markers, except HTLV-I, will be undertaken by the ATMP manufacturer; a separate blood sample will

be collected for the HTLV-I test. The date, patient name, hospital number, specimen type, staff signature, theatre number and the time collection was requested will be recorded in the specimen log located in the specimen reception area. The porter will sign the specimen log upon collection of the blood sample and it will be delivered to the onsite laboratory. On the day of procurement, the next appropriate ACI kit will be selected, the theatre number, surgeon name, patient identification sticker and Single European Code Donation Identification Sequence (SEC-DI) of the patient will be recorded in the traceability register. Once the cartilage biopsy has been procured, it will be packaged with the blood sample ready for collection by courier for transfer to the ATMP manufacturer.

The inspection consisted of a visual inspection of the theatre complex (including the main reception area where ACI kits will be delivered to and collected from), the ACI kit storage room and the specimen reception area. Round table discussions were held with the proposed DI and Corporate Licence Holder contact (CLHc), a Consultant Orthopaedic Surgeon, the Orthopaedic Theatre Matron, the Orthopaedic Lead Sister and the Advanced Therapies Pharmacist, who will all be involved in the licensable activities and wider governance procedures. The specimen log, consent form, risk assessments, training records and associated documented procedures were examined.

Inspection findings

The HTA found the proposed Designated Individual and the Licence Holder to be suitable in accordance with the requirements of the legislation.

Compliance with HTA standards

Governance and Quality

Standard	Inspection findings	Level of shortfall
GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills.		
f) There is a documented training programme that ensures that staff have adequate knowledge of the scientific and ethical principles relevant to their work, and the regulatory context.	There is no documented training programme to formalise the process of training of staff on HTA matters, including the content of the material provided to staff as part of the training. *See advice item 4*	**Minor**
g) There is a documented training programme that ensures that staff understand the organisational structure and the quality systems used within the establishment.	In addition, information on the organisational structure and quality systems used within the establishment and which relate to the licensable activities, is not documented.	

GQ4 There is a systematic and planned approach to the management of records.		
h) Raw data which are critical to the safety and quality of tissues and cells are kept for 10 years after the use, expiry date or disposal of tissues and / or cells.	There is currently no documented requirement to retain raw data for 10 years after the use, expiry date or disposal of tissues and / or cells. (e.g. temperature monitoring records).	**Minor**
GQ5 There are documented procedures for donor selection and exclusion, including donor criteria.		
b) The testing of donors by the establishment or a third party on behalf of the establishment is carried out in accordance with the requirements of Directions 002/2018.	Although the establishment intends to test all patients for HTLV-I and collect blood for this test on the day of surgery, not all of the documented procedures reflect this. For example, in the document entitled 'Protocol for management of the process of procurement of primary material for an Advanced Therapy Medicinal Product (ATMP) used in knee cartilage repair' the donor selection criteria refers to the use of a screening tool, in lieu of testing each donor.	**Minor**
GQ7 There are systems to ensure that all adverse events are investigated promptly.		
a) There are procedures for the identification, reporting, investigation and recording of adverse events and reactions, including documentation of any corrective or preventative actions.	Although the establishment has documents relating to recording incidents (Trust Incident Management and Reporting Policies, ATMP manufacturer's incident reporting form and SOP), there is no documented procedure to describe the process for identification, reporting, investigation and recording of SAEARs including the documenting of any corrective or preventative actions. There is no procedure to describe the requirement for the testing laboratory to report any serious adverse event which may influence the quality and safety of tissues and cells. *See advice item 5*	**Minor**
c) The responsibilities of personnel investigating adverse events and reactions are clearly defined.	The responsibilities of personnel investigating SAEARs have not been defined, including the responsibilities of the testing laboratory.	

GQ8 Risk assessments of the establishment's practices and processes are completed regularly and are recorded and monitored appropriately.		
a) There are documented risk assessments for all practices and processes.	Although the establishment had documented risk assessments, not all risks associated with the procedures had been considered. For example, the risk of blood samples not being collected for serology testing, the loss of serology samples, and the failure to review serology results had not been assessed.	**Minor**

Premises, Facilities and Equipment

Standard	Inspection findings	Level of shortfall
PFE1 The premises are fit for purpose.		
a) A risk assessment has been carried out of the premises to ensure that they are fit for purpose.	Although the establishment has a documented 'Environment' risk assessment, the scope does not include all risks associated with the premises and the actions taken to mitigate these risks (e.g. storage area security, temperature maintenance and monitoring).	**Minor**

Advice

The HTA advises the proposed DI to consider the following to further improve practices:

No.	Standard	Advice
1.	C3a	The proposed DI is advised to document training on how to take informed consent in accordance with the requirements of the Human Tissue (HT) Act 2004 and Code of Practice on Consent.
2.	GQ1s	The proposed DI is advised to review the agreement with the ATMP manufacturer to confirm the responsibilities of the courier in relation to serious adverse reaction or event reporting requirements.
3.	GQ2c	The proposed DI is advised to give consideration to how the independent audit will be managed to verify compliance with protocols and HTA standards. For example, consideration should be given to the scheduling of the audit, the appropriate person(s) to undertake it and the documenting of findings and corrective actions.
4.	GQ3e	The proposed DI is advised to consider retaining a copy of the training certificate received by staff completing the ATMP manufacturers training, within the staff training record.

5.	GQ7a	The proposed DI is advised to consider referencing the Trust Incident Management and Reporting Policies and ATMP manufacturer's incident reporting form and SOP, within the procedure for SAEARs management. During the discussion on SAEARs management, the establishment highlighted a document which included screenshots from the HTA SAEARs reporting portal. If the intention is for this document to form part of the procedure for incident management, the proposed DI is advised to include it within the establishment's document management system.
6.	PFE3b	The proposed DI is advised to consider including additional members of staff as points of contact via text on the wireless callout system; this would ensure actions are taken in a timely way to preserve the environment the ACI kits are stored in.

Concluding comments

Six areas of practice were identified during the inspection that require improvement, each resulting in minor shortfalls. These relate to the the governance and quality systems and premises, facilities and equipment standards. The HTA has given advice to the proposed Designated Individual with respect to the consent, governance and quality systems and premises, facilities and equipment standards.

The HTA requires that the proposed Designated Individual addresses the shortfalls by submitting a completed corrective and preventative action (CAPA) plan within 14 days of receipt of the final report (refer to Appendix 2 for recommended timeframes within which to complete actions). The HTA will then inform the establishment of the evidence required to demonstrate that the actions agreed in the plan have been completed.

The HTA has assessed the establishment as suitable to be licensed for the activities specified subject to corrective and preventative actions being implemented to meet the shortfalls identified during the inspection.

Report sent to DI for factual accuracy: 30 July 2019

Report returned from DI: 1 August 2019

Final report issued: 19 August 2019

Completion of corrective and preventative actions (CAPA) plan

Based on information provided, the HTA is satisfied that the establishment has completed the agreed actions in the CAPA plan and in doing so has taken sufficient action to correct all shortfalls addressed in the Inspection Report.

Date: 27 July 2020

Appendix 1: HTA standards

The HTA standards applicable to this establishment are shown below; those not assessed during the inspection are shown in grey text. Individual standards which are not applicable to this establishment have been excluded.

Human Tissue (Quality and Safety for Human Application) Regulations 2007 Standards

Consent

Standard
C1 Consent is obtained in accordance with the requirements of the HT Act 2004, the Human Tissue (Quality and Safety for Human Application) Regulations 2007 and as set out in the HTA's Codes of Practice.
a) If the establishment acts as a procurer of tissues and / or cells, there is an established process for acquiring donor consent which meets the requirements of the HT Act 2004 the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (Q&S Regulations) and the HTA's Codes of Practice
c) The establishment or the third party's procedure on obtaining donor consent includes how potential donors are identified and who is able to take consent.
d) Consent forms comply with the HTA Codes of Practice.
e) Completed consent forms are included in records and are made accessible to those using or releasing tissue and / or cells for a Scheduled Purpose.
C2 Information about the consent process is provided and in a variety of formats.
a) The procedure on obtaining consent details what information will be provided to donors. As a minimum, the information specified by Directions 002/2018 is included.
c) Information is available in suitable formats and there is access to independent interpreters when required.
d) There are procedures to ensure that information is provided to the donor or donor's family by trained personnel.
C3 Staff involved in seeking consent receive training and support in the implications and essential requirements of taking consent.
a) Staff involved in obtaining consent are provided with training on how to take informed consent in accordance with the requirements of the HT Act 2004 and Code of Practice on Consent.
b) Training records are kept demonstrating attendance at training on consent.

Governance and Quality

Standard
GQ1 All aspects of the establishment's work are supported by ratified documented policies and procedures as part of the overall governance process.
a) There is an organisational chart clearly defining the lines of accountability and reporting relationships.

b) There are procedures for all licensable activities that ensure integrity of tissue and / or cells and minimise the risk of contamination.
c) There are regular governance meetings, for example health and safety, risk management and clinical governance committees, which are recorded by agendas and minutes.
d) There is a document control system to ensure that changes to documents are reviewed, approved, dated and documented by an authorised person and only current documents are in use.
e) There are procedures for tissue and / or cell procurement, which ensure the safety of living donors.
h) There are procedures for the management and quarantine of non-conforming consignments or those with incomplete test results, to ensure no risk of cross contamination.
i) There are procedures to ensure tissues and / or cells are not released from quarantine until verification has been completed and recorded.
j) There are procedures detailing the critical materials and reagents used and where applicable, materials and reagents meet the standards laid down by the European directives on medical devices and in vitro diagnostic medical devices.
l) There are procedures to ensure that in the event of termination of activities for whatever reason, stored tissues and / or cells are transferred to another licensed establishment or establishments.
m) The criteria for allocating tissues and / or cells to patients and health care institutions are documented and made available to these parties on request.
o) There is a complaints system in place.
p) There are written agreements with third parties whenever an activity takes place that has the potential to influence the quality and safety of human tissues and / or cells.
q) There is a record of agreements established with third parties.
r) Third party agreements specify the responsibilities of the third party and meet the requirements set out in Directions 002/2018.
s) Third party agreements specify that the third party will inform the establishment in the event of a serious adverse reaction or event.
t) There are procedures for the re-provision of service in an emergency.
GQ2 There is a documented system of quality management and audit.
a) There is a quality management system which ensures continuous and systematic improvement.
b) There is an internal audit system for all licensable activities.
c) An audit is conducted in an independent manner at least every two years to verify compliance with protocols and HTA standards, and any findings and corrective actions are documented.
GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills.
a) There are clearly documented job descriptions for all staff.
b) There are orientation and induction programmes for new staff.

c) There are continuous professional development (CPD) plans for staff and attendance at training is recorded.
d) There is annual documented mandatory training (e.g. health and safety and fire).
e) Personnel are trained in all tasks relevant to their work and their competence is recorded.
f) There is a documented training programme that ensures that staff have adequate knowledge of the scientific and ethical principles relevant to their work, and the regulatory context.
g) There is a documented training programme that ensures that staff understand the organisational structure and the quality systems used within the establishment.
h) There is a system of staff appraisal.
i) Where appropriate, staff are registered with a professional or statutory body.
j) There are training and reference manuals available.
k) The establishment is sufficiently staffed to carry out its activities.
GQ4 There is a systematic and planned approach to the management of records.
a) There are procedures for the creation, identification, maintenance, access, amendment, retention and destruction of records.
b) There is a system for the regular audit of records and their content to check for completeness, legibility and accuracy and to resolve any discrepancies found.
c) Written records are legible and indelible. Records kept in other formats such as computerised records are stored on a validated system.
d) There is a system for back-up / recovery in the event of loss of computerised records.
e) The establishment keeps a register of the types and quantities of tissues and / or cells that are procured, tested, preserved, processed, stored and distributed or otherwise disposed of, and on the origin and destination of tissues and cells intended for human application.
f) There are procedures to ensure that donor documentation, as specified by Directions 002/2018, is collected and maintained.
g) There is a system to ensure records are secure and that donor confidentiality is maintained in accordance with Directions 002/2018.
h) Raw data which are critical to the safety and quality of tissues and cells are kept for 10 years after the use, expiry date or disposal of tissues and / or cells.
i) The minimum data to ensure traceability from donor to recipient as required by Directions 002/2018 are kept for 30 years after the use, expiry or disposal of tissues and / or cells.
j) Records are kept of products and material coming into contact with the tissues and / or cells.
m) In the event of termination of activities of the establishment a contingency plan to ensure records of traceability are maintained for 10 or 30 years as required.

GQ5 There are documented procedures for donor selection and exclusion, including donor criteria.
a) Donors are selected either by the establishment or the third party acting on its behalf in accordance with the criteria required by Directions 002/2018.
b) The testing of donors by the establishment or a third party on behalf of the establishment is carried out in accordance with the requirements of Directions 002/2018.
d) There is a system in place either at the establishment or at a third party acting on its behalf to record results of donor selection and associated tests.
e) Testing of donor samples is carried out using CE marked diagnostic tests.
f) Samples taken for donor testing are clearly labelled with the time and place the sample was taken and a unique donor identification code.
GQ6 A coding and records system facilitates traceability of tissues and / or cells, ensuring a robust audit trail.
a) There is a donor identification system which assigns a unique code to each donation and to each of the products associated with it.
b) An audit trail is maintained, which includes details of when the tissues and / or cells were acquired and from where, the uses to which the tissues and / or cells were put, when the tissues and / or cells were transferred elsewhere and to whom.
c) The establishment has procedures to ensure that tissues and / or cells imported, procured, processed, stored, distributed and exported are traceable from donor to recipient and vice versa.
d) The requirements of the Single European Code are adhered to as set out in Directions 002/2018.
GQ7 There are systems to ensure that all adverse events, reactions and/or incidents are investigated promptly.
a) There are procedures for the identification, reporting, investigation and recording of adverse events and reactions, including documentation of any corrective or preventative actions.
b) There is a system to receive and distribute national and local information (e.g. HTA regulatory alerts) and notify the HTA and other establishments as necessary of serious adverse events or reactions.
c) The responsibilities of personnel investigating adverse events and reactions are clearly defined.
d) There are procedures to identify and decide the fate of tissues and / or cells affected by an adverse event, reaction or deviation from the required quality and safety standards.
GQ8 Risk assessments of the establishment’s practices and processes are completed regularly and are recorded and monitored appropriately.
a) There are documented risk assessments for all practices and processes.
b) Risk assessments are reviewed regularly, as a minimum annually or when any changes are made that may affect the quality and safety of tissues and cells.
c) Staff can access risk assessments and are made aware of local hazards at training.

d) A documented risk assessment is carried out to decide the fate of any tissue and / or cells stored prior to the introduction of a new donor selection criteria or a new processing step, which enhances the quality and safety of tissue and / or cells.

Premises, Facilities and Equipment

Standard
PFE1 The premises are fit for purpose.
a) A risk assessment has been carried out of the premises to ensure that they are fit for purpose.
b) There are procedures to review and maintain the safety of staff, visitors and patients.
c) The premises have sufficient space for procedures to be carried out safely and efficiently.
e) There are procedures to ensure that the premises are secure and confidentiality is maintained.
f) There is access to a nominated, registered medical practitioner and / or a scientific advisor to provide advice and oversee the establishment's medical and scientific activities.
PFE2 Environmental controls are in place to avoid potential contamination.
c) There are procedures for cleaning and decontamination.
d) Staff are provided with appropriate protective clothing and equipment that minimise the risk of contamination of tissue and / or cells and the risk of infection to themselves.
PFE3 There are appropriate facilities for the storage of tissues and / or cells, consumables and records.
a) Tissues, cells, consumables and records are stored in secure environments and precautions are taken to minimise risk of damage, theft or contamination.
b) There are systems to deal with emergencies on a 24 hour basis.
c) Tissues and / or cells are stored in controlled, monitored and recorded conditions that maintain tissue and / or cell integrity.
PFE4 Systems are in place to protect the quality and integrity of tissues and / or cells during transport and delivery to its destination.
b) There are procedures for the transport of tissues and / or cells which reflect identified risks associated with transport.
c) There is a system to ensure that traceability of tissues and / or cells is maintained during transport.
d) Records are kept of transportation and delivery.
e) Tissues and / or cells are packaged and transported in a manner and under conditions that minimise the risk of contamination and ensure their safety and quality.
f) There are third party agreements with courier or transport companies to ensure that any specific transport conditions required are maintained.
g) Critical transport conditions required to maintain the properties of tissue and / or cells are defined and documented.

h) Packaging and containers used for transportation are validated to ensure they are fit for purpose.
i) Primary packaging containing tissues and / or cells is labelled with the information required by Directions.
j) Shipping packaging containing tissues and / or cells is labelled with the information required by Directions.
PFE5 Equipment is appropriate for use, maintained, quality assured, validated and where appropriate monitored.
a) Critical equipment and technical devices are identified, validated, regularly inspected and records are maintained.
b) Critical equipment is maintained and serviced in accordance with the manufacturer's instructions.
e) There are documented agreements with maintenance companies.
f) Cleaning, disinfection and sanitation of critical equipment is performed regularly and this is recorded.
g) Instruments and devices used for procurement are sterile, validated and regularly maintained.
h) Users have access to instructions for equipment and receive training in the use of equipment and maintenance where appropriate.
i) Staff are aware of how to report an equipment problem.
j) For each critical process, the materials, equipment and personnel are identified and documented.
k) There are contingency plans for equipment failure.

Appendix 2: Classification of the level of shortfall (HA)

Where the HTA determines that a licensing standard is not met, the improvements required will be stated and the level of the shortfall will be classified as 'Critical', 'Major' or 'Minor'. Where the HTA is not presented with evidence that an establishment meets the requirements of an expected standard, it works on the premise that a lack of evidence indicates a shortfall.

The action an establishment will be required to make following the identification of a shortfall is based on the HTA's assessment of risk of harm and/or a breach of the HT Act or associated Directions.

1. **Critical shortfall:**

   A shortfall which poses a significant direct risk of causing harm to a recipient patient or to a living donor,

   Or

   A number of 'major' shortfalls, none of which is critical on its own, but viewed cumulatively represent a systemic failure and therefore are considered 'critical'.

   A critical shortfall may result in one or more of the following:

   (1) A notice of proposal being issued to revoke the licence

(2) Some or all of the licensable activity at the establishment ceasing with immediate effect until a corrective action plan is developed, agreed by the HTA and implemented.

(3) A notice of suspension of licensable activities

(4) Additional conditions being proposed

(5) Directions being issued requiring specific action to be taken straightaway

2. Major shortfall:

A non-critical shortfall.

A shortfall in the carrying out of licensable activities which poses an indirect risk to the safety of a donor or a recipient

or

A shortfall in the establishment's quality and safety procedures which poses an indirect risk to the safety of a donor or a recipient;

or

A shortfall which indicates a major deviation from the Human Tissue (Quality and Safety for Human Application) Regulations 2007 or the HTA Directions;

or

A shortfall which indicates a failure to carry out satisfactory procedures for the release of tissues and cells or a failure on the part of the designated individual to fulfil his or her legal duties;

or

A combination of several 'minor' shortfalls, none of which is major on its own, but which, viewed cumulatively, could constitute a major shortfall by adversely affecting the quality and safety of the tissues and cells.

In response to a major shortfall, an establishment is expected to implement corrective and preventative actions within 1-2 months of the issue of the final inspection report. Major shortfalls pose a higher level of risk and therefore a shorter deadline is given, compared to minor shortfalls, to ensure the level of risk is reduced in an appropriate timeframe.

3. Minor shortfall:

A shortfall which cannot be classified as either critical or major and, which can be addressed by further development by the establishment.

This category of shortfall requires the development of a corrective action plan, the results of which will usually be assessed by the HTA either by desk based review or at the time of the next inspection.

In response to a minor shortfall, an establishment is expected to implement corrective and preventative actions within 3-4 months of the issue of the final inspection report.

Follow up actions

A template corrective and preventative action plan will be sent as a separate Word document with both

the draft and final inspection report. You must complete this template and return it to the HTA within 14 days of the issue of the final report.

Based on the level of the shortfall, the HTA will consider the most suitable type of follow-up of the completion of the corrective and preventative action plan. This may include a combination of

- a follow-up site-visit inspection
- a request for information that shows completion of actions
- monitoring of the action plan completion
- follow up at next desk-based or site-visit inspection.

After an assessment of your proposed action plan you will be notified of the follow-up approach the HTA will take.